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10/594,851	05/04/2007	Dominique Cheneval	608352000101	2057
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MORRISON & FOERSTER LLP 755 PAGE MILL RD PALO ALTO, CA 94304-1018			EXAMINER HIBBERT, CATHERINE S	
			ART UNIT 1636	PAPER NUMBER
			NOTIFICATION DATE 03/24/2011	DELIVERY MODE ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	<b>Application No.</b> 10/594,851	<b>Applicant(s)</b> CHENEVAL ET AL.	
	<b>Examiner</b> CATHERINE HIBBERT	<b>Art Unit</b> 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 17 November 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 10-13, 18 and 23-39 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 10-13, 18 and 23-39 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 26 September 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☒ Certified copies of the priority documents have been received in Application No. 09/869,159.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>2/25/2009</u> .   | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

This is the First Office Action on the Merits of US 10/594,851 filed 9/29/2006 which is a national stage entry of PCT/CA05/00491 filed 4/1/2005, which is a Continuation of US Application 10/814,634 filed 4/1/2004 (now US Patent 7,598,079), which is a Continuation-In-Part of US Application 09/869,159 filed Dec. 23, 1999 which claims the benefit of Foreign Priority of UK Patent Application No. 9828709.7 filed 24 December 1998.

Applicant's Amendment to the Specification filed 11/17/2010 and Amendment to the Claims filed 11/16/2009 are received and entered. Claims 1-9, 14-17 and 19-22 are cancelled. Claims 23-39 are new. Claims 10, 11, 12 and 18 are amended. Claims 10-13, 18 and 23-39 are pending and under examination.

### **Election/Restriction**

Applicant's election of Group III and rejoined Group VI in the reply filed on 16 November 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

### **Priority**

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/869,159, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Claims 10-13, 18 and 23-39 are directed to methods which recite the term "CRD" which is not disclosed in the '159 application . As such, claims receive priority to the filing date of the parent application 10/814,634, filed 4/1/2004.

### **Specification**

The disclosure is objected to because of the following informalities: In the brief description of the drawings on page 7 of the instant application, there is a reference to a 30 bp fragment in figure 2; however, the fragment in figure 2 appears to be 40 bp, not 30 bp.

Appropriate correction is required.

### **;Claim Rejections - 35 USC § 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10-13 and 23-39 rejected under 35 U.S.C. 103(a) as being unpatentable over Zubiaga et al. (1995, MCB, Vol 15, No.4, pages 2219-2230; of record in the IDS), in view of Banholzer et al (Molecular Cellular Biology, 1997, Vol 17, No.6, pages 3254-3260; of record in the IDS), in view of Lemm and Ross (Molecular and Cellular Biology, 2002, Vol 22, No. 12, pages 3959-3969; of record in the IDS).

Claims 10-13 and 23-39 are drawn to a method of screening for one or more compound which affect mRNA stability comprising the steps of:

- i) contacting a DNA expression system with at least one test compound under conditions whereby, in the absence of the test compound, said DNA expression system expresses a protein having a detectable signal, wherein the mRNA which is transcribed from said expression system and encodes said protein comprises at least one copy of a heterologous mRNA instability sequence comprising one or more coding region determinant (CRD) or a fragment thereof;
- (ii) measuring said detectable signal; and
- (iii) comparing the measured detectable signal with a control, wherein a decrease in the measured detectable signal compared to said control indicates a compound that decreases mRNA

stability and an increase in the measured detectable signal compared to said control indicates a compound that increases mRNA stability.

Claim 11 specifies that the control comprises measuring the detectable signal from the DNA expression system in the absence of the test compound.

Claim 12 specifies that the control comprises contacting a control expression system capable of expressing a second protein having a second detectable signal with the test compound and measuring said second detectable signal.

Claim 13 specifies that the compounds are being screened for their ability to induce mRNA degradation, and wherein a decrease in the measured detectable signal compared to said control indicates a compound that induces mRNA degradation.

Claim 26 specifies that the heterologous mRNA instability sequence is inserted into the 3'UTR of the gene encoding the protein having a detectable signal.

Claims 23 /24/25 specify that the heterologous mRNA instability sequence is derived from a naturally occurring source gene/encoding a protein implicated in a disease of interest/c-myc. Claim 27 specifies within claim 23, that the heterologous mRNA instability sequence further comprises DNA corresponding to the regions that flank said CRD or fragment thereof in the naturally occurring source gene or mRNA. Claim 28 specifies within claim 27 that the heterologous mRNA instability sequence is inserted into the 3'UTR of the gene encoding the protein having a detectable signal.

Claims 29/30/31 specify that the protein having a detectable signal is an enzyme/ luciferase or  $\beta$ -galactosidase/ is a fluorescent or phosphorescent protein.

Claims 18 and 32-39 are drawn to a high throughput method for screening libraries of compounds to identify compounds that affect the stability of mRNA comprising:

(i) inoculating wells of one or more multi-well plates comprising a growth medium with a stably transfected cell line comprising a DNA expression vector, which in the absence of a test compound expresses a protein having a detectable signal, wherein the mRNA which is transcribed from said expression vector and encodes said protein comprises at least one copy of a heterologous mRNA instability sequence comprising one or more coding region determinant (CRD) or a fragment thereof;

(ii) maintaining the one or more multi-well plates under conditions that allow cells of the cell line to grow and express the protein having a detectable signal;

(iii) contacting the cells with one or more test compound;

(iv) measuring the detectable signal; and

(v) comparing the measured detectable signal with a control; wherein a decrease in the measured detectable signal compared to the control indicates a compound that decreases mRNA stability and an increase in the measured detectable signal compared to the control indicates a compound that increases mRNA stability.

Claim 32 specifies that the control comprises measuring the detectable signal from the stably transfected cell line in the absence of said test compound.

Claim 33 specifies that the stably transfected cell line comprises a second DNA expression vector capable of expressing a second protein having a second detectable signal, and wherein said control comprises measuring the second detectable signal.

Claim 34 specifies that the compounds are being screened for their ability to induce mRNA degradation, and wherein a decrease in the measured detectable signal compared to said control indicates a compound that induces mRNA degradation.

Claims 35/36 specify that the heterologous mRNA instability sequence is derived from a naturally occurring source gene/ c-myc.

Claim 37 specifies that the heterologous mRNA instability sequence is inserted into the 3'UTR of the gene encoding the protein having a detectable signal.

Claim 38 specifies within claim 35, that the heterologous mRNA instability sequence further comprises DNA corresponding to the regions that flank the CRD or fragment thereof in the naturally occurring source gene or mRNA. Claim 39 specifies that the heterologous mRNA instability sequence is inserted into the 3'UTR of the gene encoding the protein having a detectable signal.

**Zubiaga et al** disclose an expression vector comprising c-fos promoter operatively linked to globin gene, wherein several ARE isolated from c-fos is inserted into 3'UTR of the globin gene (see page 2220, 2nd col., 6th paragraph), resulting in sets of cell lines comprises different expression constructs. Zubiaga et al. also disclose that a control plasmid pRSV-lacZ, comprising a gene coding for expression of lacZ, 5'and 3'UTR for expression of said gene without mRNA instability sequence (see page 2221, 1st col., 2nd paragraph, lines 4-9). Zubiaga et al. further disclose that these construct are co-transfected into NIH-3T3 cells (see page 2221, 1st CO1., 2nd paragraph, lines 1-4).

**Banholzer et al** disclose that rapamycin promotes degradation of IL-3 transcripts at posttranscriptional level via 3' UTR (see page 3257, 2nd col., 1st paragraph). Banholzer et al.

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disclose two cell lines stably transfected with IL-3 expression system either with (VD1-M1) or without (VD1-M1AAU) mRNA instability sequence (3' UTR) (see page 3256, 1st col., lines 1-3). Banholzer et al. also disclose that following rapamycin and FK506 treatment, endogenous and exogenous wild type IL-3 decayed with very similar kinetics (see Figure 3b, left panel) whereas the exogenous mutant IL-3 mRNA level is not affected by either compound (Figure 3b, right panel, and 3c). The method and assay system disclosed by Banholzer et al. identifies rapamycin and FK506 as compounds that induce mRNA degradation.

However, Zubiaga et al do not teach an assay system for screening compounds which destabilize mRNA that comprises a stably transfected cell line as claimed and a test compound.

It would have been obvious for one of ordinary skill in the art to develop an assay system as taught by Banholzer that is able to screen compounds such as rapalogs for their ability to modulating the mRNA instability sequence. Based on the teaching of Zubiaga, those of ordinary skill in the would have been motivated to screen compounds that would affect ARE sequence instability using the heterologous expression construct as disclosed in Zubiaga et al.

One of ordinary skill in the art would also be motivated to use stably transfected cell lines because they are easy to maintain such that one does not have to do transfection every time to test a compound. The level of skill in the art is high. Absent evidence from the contrary, one of ordinary skilled in the art would have reasonable expectation of success to use the cell line taught by Zubiaga as a system to test compounds and make the cell line a stably transfected cell for said purpose. Therefore, the claimed invention would have been prima facie obvious at the time the invention was made.

In addition, neither references of Zubiaga and Banholzer explicitly teach a coding region instability determinant as the instability sequence.

**Lemm and Ross** teach a 249 nucleotide coding region from c-myc destabilizes c-myc mRNA: Lemm and Ross also teach that said nucleotide sequence destabilizes beta-globin mRNA when inserted in frame within the coding region of said beta-globin gene (see page 3959, 2nd CO1., 2nd paragraph).

It would have been obvious to one of ordinary skill in the art to use the cell lines with constructs that have instability sequence as taught by either Zubiaga et al. or Banholzer et al. to test compounds that affect coding region instability determinants (CRD) from c-myc. One of ordinary skill in the art would have been motivated to do so for screening compounds that modulates the activity of the CRD. Absent evidence from the contrary, the ordinary artisan would have reasonable expectation of success to insert the CRD into a construct which can then be transfected into a cell line for testing compounds. Therefore, the invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

### **Claim Rejections - 35 USC § 112**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23-25 and 35-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 23 and 35 recite the term "derived" which renders the claims indefinite because the nature and number of derivative process is unknown. As such, the metes and bounds of the

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claim cannot be established. Claims 24-25 and 36 are indefinite insofar as they depend from claims 23 and 35.

### **Conclusion**

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CATHERINE HIBBERT whose telephone number is (571)270-3053. The examiner can normally be reached on M-F 8AM-5PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joanne Hama can be reached on 571-272-2911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NANCY VOGEL/

Primary Examiner, Art Unit 1636

Catherine Hibbert  
Examiner AU1636